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Patentanmeldung Nr. Patent application No. Demande de brevet n°

03027050.8

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Bezeichnung der Erfindung/Title of the invention/Titre de l'invention:  
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Cyclopentyl Derivatives

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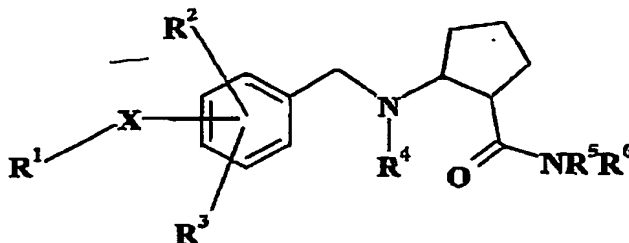
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## CYCLOPENTYL DERIVATIVES

This invention is related to novel cyclopentyl derivatives of the following general formula (I)



I

wherein

X is methylene, oxygen, sulphur or a  $\text{NR}^7$  group;

$\text{R}^1$  is a straight or branched  $\text{C}_1\text{-C}_8$  alkyl or  $\text{C}_3\text{-C}_8$  alkenylene or  $\text{C}_3\text{-C}_8$  alkynylene chain, optionally substituted with  $\text{CF}_3$ , phenyl, phenoxy or naphthyl, the aromatic rings optionally substituted by one or more  $\text{C}_1\text{-C}_4$  alkyl, halogens, trifluoromethyl, hydroxy or  $\text{C}_1\text{-C}_4$  alkoxy groups;

$\text{R}^2, \text{R}^3$  are independently hydrogen, a  $\text{C}_1\text{-C}_3$  alkyl chain, halogen, trifluoromethyl, hydroxy or  $\text{C}_1\text{-C}_4$  alkoxy groups;

$\text{R}^4, \text{R}^5, \text{R}^6, \text{R}^7$  are independently hydrogen or  $\text{C}_1\text{-C}_6$  alkyl;

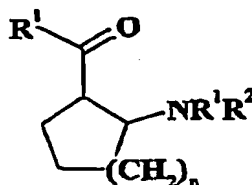
and the pharmaceutically acceptable salts thereof, that are active as sodium and/or calcium channel modulators and therefore useful in preventing, alleviating and curing a wide range of pathologies, including, but not limited to, neurological, psychiatric, cardiovascular, inflammatory, ophthalmic, urologic, metabolic and gastrointestinal diseases, where the above mechanisms have been described as playing a pathological role.

## BACKGROUND OF THE INVENTION

### Chemical background

DE 2624290 describes 2-aminocycloalkanecarboxylic acids and their derivatives with the general formula

5



wherein R¹ is a hydroxyl or a NR⁴R⁵ group, R² and R³ are hydrogen, alkyl, aralkyl, aryl or acyl, R⁴ and R⁵ are hydrogen, C₁-C₈ alkyl, aralkyl, aryl or heteroaryl, and their use as analgesics, antipyretics, and anesthetics.

10

### Biological background

It is well known that sodium channels play an important role in the neuronal network by transmitting electrical impulses rapidly throughout cells and cell networks, thereby coordinating higher processes ranging from locomotion to cognition. These channels are large transmembrane proteins, which are able to switch between different states to enable selective permeability for sodium ions. For this process an action potential is needed to depolarize the membrane, and hence these channels are voltage-gated. In the past few years a much better understanding of sodium channels and drugs interacting with them has been developed.

20

It has become clear that a number of drugs having an unknown mechanism of action actually act by modulating sodium channel conductance, including local anesthetics, class I antiarrhythmics and anticonvulsants. Neuronal sodium channel blockers have found application with their use in the treatment of epilepsy (phenytoin and carbamazepine), bipolar disorder (lamotrigine), preventing neurodegeneration, and in reducing neuropathic pain. Various anti-epileptic drugs that stabilize neuronal excitability are

25

effective in neuropathic pain (gabapentin).

In addition, an increase in sodium channel expression or activity has also been observed in several models of inflammatory pain, suggesting a role of sodium channels in inflammatory pain.

5        Calcium channels are membrane-spanning, multi-subunit proteins that  
allow controlled entry of calcium ions into cells from the extracellular fluid.  
Commonly, calcium channels are voltage dependent and are referred to as  
voltage sensitive calcium channels (VSCC). VSCCs are found throughout the  
mammalian nervous system, where they regulate such varied activities as  
10 cellular excitability, transmitter release, intracellular metabolism,  
neurosecretory activity and gene expression. All "excitable" cells in animals,  
such as neurons of the central nervous system (CNS), peripheral nerve cells,  
and muscle cells, including those of skeletal muscles, cardiac muscles and  
venous and arterial smooth muscles, have voltage dependent calcium  
15 channels. Calcium channels have a central role in regulating intracellular  
calcium ions levels that are important for cell viability and function.  
Intracellular calcium ion concentrations are implicated in a number of vital  
processes in animals, such as neurotransmitter release, muscle contraction,  
pacemaker activity, and secretion of hormones. It is believed that calcium  
20 channels are relevant in certain disease states. A number of compounds useful  
in treating various cardiovascular diseases in mammals, including humans, are  
thought to exert their beneficial effects by modulating functions of voltage  
dependant calcium channels present in cardiac and/or vascular smooth muscle.  
Compounds with activity against calcium channels have also been implicated  
25 for the treatment of pain. In particular N-type calcium channels (Cav2.2),  
responsible for the regulation of neurotransmitters, are thought to play a  
significant role in nociceptive transmission, both due to their tissue  
distribution as well as from the results of several pharmacological studies.

This hypothesis has been validated in the clinic by Zinocotide, a peptide derived from the venom of the marine snail, *Conus Magus*. A limitation in the therapeutic use of this peptide is that it has to be administered intrathecally in humans (Bowersox S. S. and Luther R. *Toxicon*, 1998, 36, 11, 1651-1658).

5 All together these findings indicate that compounds with sodium and/or calcium channel blockade have a high therapeutic potential in preventing, alleviating and curing a wide range of pathologies, including neurological, psychiatric, cardiovascular, urologic, metabolic and gastrointestinal diseases, where the above mechanisms have been described as playing a pathological role.

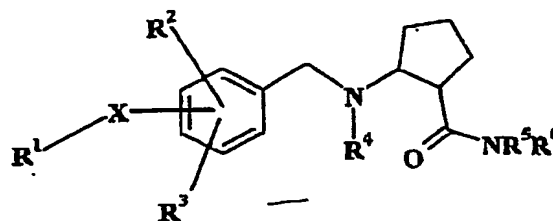
10 There are many papers and patents which describe sodium channel and/or calcium channel modulators or antagonists for the treatment or modulation of a plethora of disorders, such as their use as local anesthetics, antiarrhythmics, antiemetics, antimanic depressants, agents for the treatment of unipolar depression, cardiovascular diseases, urinary incontinence, diarrhea,  
15 inflammation, epilepsy, neurodegenerative conditions, nerve cell death, anticonvulsants, neuropathic pain, migraine, acute hyperalgesia and inflammation, renal disease, allergy, asthma, bronchospasm, dysmenorrhea, esophageal spasm, glaucoma, urinary tract disorders, gastrointestinal motility disorders, premature labour, obesity. A largely incomplete list is shown below.

20 An extensive and thorough prior art overview is reported in WO 03/057219 (and references therein); a further selection of prior art is reported in the following references: Alzheimer, C. *Adv. Exp. Med. Biol.* 2002, 513, 161-181; Vanegas, H.; Schaible, H. *Pain* 2000, 85, 9-18; U.S. Patent 5,051,403; U.S. Patent 5,587,454; U.S. Patent 5,863,952; U.S. Patent  
25 6,011,035; U.S. Patent 6,117,841; U.S. Patent 6,362,174; U.S. Patent 6,380,198; U.S. Patent 6,420,383; U.S. Patent 6,458,781; U.S. Patent 6,472,530; U.S. Patent 6,518,288; U.S. Patent 6,521,647; WO 97/10210; WO 03/018561.

5

**DESCRIPTION OF THE INVENTION**

The present invention provides novel compounds of formula I



I

wherein

**X** is methylene, oxygen, sulphur or a NR<sup>7</sup> group;

**R<sup>1</sup>** is a straight or branched C<sub>1</sub>-C<sub>8</sub> alkyl or C<sub>3</sub>-C<sub>8</sub> alkenylene or C<sub>3</sub>-C<sub>8</sub> alkynylene chain, optionally substituted with CF<sub>3</sub>, phenyl, phenoxy or naphthyl, the aromatic rings optionally substituted by one or more C<sub>1</sub>-C<sub>4</sub> alkyl, halogens, trifluoromethyl, hydroxy or C<sub>1</sub>-C<sub>4</sub> alkoxy groups;

**R<sup>2</sup>, R<sup>3</sup>** are independently hydrogen, a C<sub>1</sub>-C<sub>3</sub> alkyl chain, halogen, trifluoromethyl, hydroxy or C<sub>1</sub>-C<sub>4</sub> alkoxy groups;

**R<sup>4</sup>, R<sup>5</sup>, R<sup>6</sup>, R<sup>7</sup>** are independently hydrogen or C<sub>1</sub>-C<sub>6</sub> alkyl;

and the pharmaceutically acceptable salts thereof.

The compounds of the invention are useful as sodium and/or calcium channel modulators.

The substituents R<sup>1</sup>-X, R<sup>2</sup> and R<sup>3</sup> in the phenyl ring may be in any position. The pharmaceutically acceptable salts of the compounds of formula I include acid addition salts with inorganic, e.g. hydrochloric, hydrobromic, sulphuric, and phosphoric acids or organic, e.g. acetic, propionic, benzoic, cinnamic, mandelic, salicylic, glycolic, lactic, oxalic, malic, maleic, malonic, fumaric, tartaric, citric, and the like.



Preferred compounds of the invention are the compounds of formula I, wherein X is oxygen, methylene, NH or NCH<sub>3</sub>, R<sup>1</sup> is C<sub>1</sub>-C<sub>8</sub> alkyl chain, optionally substituted with CF<sub>3</sub>, phenyl or phenoxy group, where the aromatic ring in R<sup>1</sup> is optionally substituted by one or two halogen or methoxy or trifluoromethyl groups, R<sup>2</sup> and R<sup>3</sup> are hydrogen, methyl, methoxy, fluorine, chlorine or bromine, R<sup>4</sup>, R<sup>5</sup> and R<sup>6</sup> are hydrogen or methyl.

Examples of specific compounds of the invention are:

- 2-(2-benzyloxy-benzylamino)-cyclopentane carboxylic acid amide;
- 2-(3-benzyloxy-benzylamino)-cyclopentane carboxylic acid amide;
- 10 2-(4-benzyloxy-benzylamino)-cyclopentane carboxylic acid amide;
- 2-[2-(2-Fluoro-benzyloxy)-benzylamino]-cyclopentane carboxylic acid amide;
- 2-[3-(2-Fluoro-benzyloxy)-benzylamino]-cyclopentane carboxylic acid amide;
- 15 *cis*-2-[3-(2-Fluoro-benzyloxy)-benzylamino]-cyclopentane carboxylic acid amide;
- 2-[4-(2-Fluoro-benzyloxy)-benzylamino]-cyclopentane carboxylic acid amide;
- 2-[4-(2-Fluoro-benzylthio)-benzylamino]-cyclopentane carboxylic acid amide;
- 20 2-[4-(2-Fluoro-benzylamino)-benzylamino]-cyclopentane carboxylic acid amide;
- 2-[2-(2-Fluoro-benzyloxy)-3-fluoro-benzylamino]-cyclopentane carboxylic acid amide;
- 25 2-[4-(2-Fluoro-benzyloxy)-3-fluoro-benzylamino]-cyclopentane carboxylic acid amide;
- 2-[2-(2-Fluoro-benzyloxy)-3-chloro-benzylamino]-cyclopentane carboxylic acid amide;

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(2-[4-(2-Fluoro-benzyloxy)-3-chloro-benzylamino]-cyclopentane  
carboxylic acid amide;

(2-[4-(2-Fluoro-benzyloxy)-3-bromo-benzylamino]-cyclopentane  
carboxylic acid amide;

5 (2-[4-(2-Fluoro-benzyloxy)-2-methoxy-benzylamino]-cyclopentane  
carboxylic acid amide;

(2-[4-(2-Fluoro-benzyloxy)-3-methoxy-benzylamino]-cyclopentane  
carboxylic acid amide;

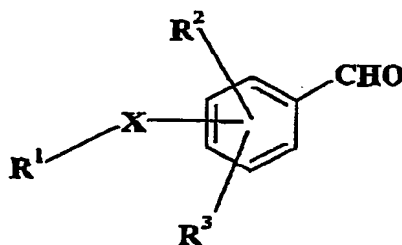
2-[4-(2-Fluoro-benzyloxy)-3,5-dimethyl-benzylamino]-cyclopentane  
10 carboxylic acid amide;

*cis*-2-[4-(2-Fluoro-benzyloxy)-3,5-dimethyl-benzylamino]-cyclopentane  
carboxylic acid amide;

and all the stereoisomers and/or pharmaceutically acceptable salts thereof.

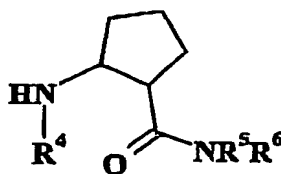
The compounds of the invention and the salts thereof can be obtained  
15 by a process comprising:

a) reaction of compounds of formula II



II

20 wherein  $R^1$ ,  $R^2$ ,  $R^3$  and X are as defined above  
with compounds of formula III, in the presence of a reducing agent

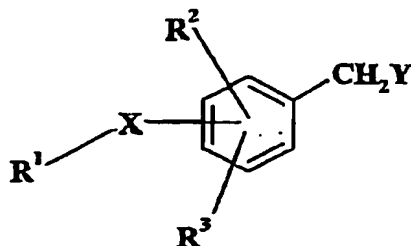


III

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wherein  $R^4$ ,  $R^5$  and  $R^6$  as defined previously thus obtaining a compound of formula I; or

b) reaction of compounds of formula IV

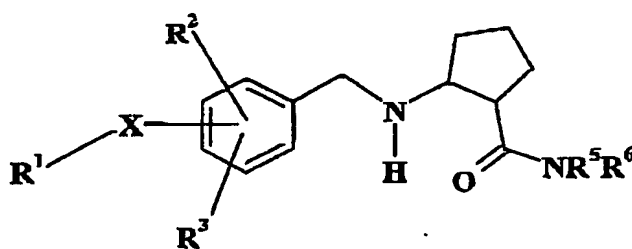


IV

wherein  $R^1$ ,  $R^2$ ,  $R^3$  and X are as defined above and Y is a halogen atom or a O-EWG group, where the EWG means an electron withdrawing group, like e.g. mesyl, tosyl or trifluoroacetyl groups, able to transform the oxygen which they are linked to, in a good leaving group

with compounds of formula III thus obtaining a compound of formula I; or

c) reacting of a compound of formula Ia



Ia

wherein  $R^1$ ,  $R^2$ ,  $R^3$ ,  $R^5$ ,  $R^6$  and X are as defined above, with compounds of formula V or VI



V



VI

wherein Y and  $R^4$  are as defined above; and  $R^8$  is hydrogen or  $C_1$ - $C_5$  alkyl, thus obtaining a compound of the invention in which  $R^4$  is  $C_1$ - $C_6$  alkyl;

and, if desired, converting a compound of the invention into another compound of the invention and/or, if desired, converting a compound of the invention into a pharmaceutically acceptable salt and/or, if desired, converting a salt into a free compound and/or, if desired, separating a mixture of isomers  
5 of compounds of the invention into a single isomer.

Compounds II, III, IV, V and VI are commercially available compounds or are prepared from commercially available compounds using well-known methods.

The reactions of compounds of formula II with compounds of formula  
10 III and of compounds of formula Ia with compounds of formula VI to give the compounds of formula I is a reductive amination reaction which can be carried out according to well known methods. According to a preferred embodiment of the invention, it may be performed under nitrogen atmosphere, in a suitable organic solvent, such as an alcohol, e.g. a lower alkanol, in  
15 particular methanol, or in acetonitrile, or in tetrahydrofuran, at a temperature ranging from about 0°C to about 80°C, in the presence of a reducing agent, the most appropriate being sodium borohydride or sodium cyanoborohydride. Occasionally Titanium IV isopropylate and molecular sieves can be added to the reaction mixture for facilitating the reaction.

20 In a compound of formula IV and V the halogen is preferably bromine or iodine. The alkylation reactions of a compound of formula IV with a compound of formula III and of a compound of formula Ia with a compound of formula V can be carried out in a suitable organic solvent, such as an alcohol, e.g. methanol, ethanol or isopropanol, in particular in ethanol, at a  
25 temperature ranging from about 0°C to about 50°C.

When in the compounds of the present invention and in the intermediate-products thereof, groups are present, which need to be protected before submitting them to the above illustrated reactions, they may be

protected before being reacted and then deprotected according to well-known methods.

## PHARMACOLOGY

The compounds of the invention display affinities for the calcium  
5 and/or sodium channel binding sites as demonstrated using selective  
radioligands in *in vitro* binding studies.

The compounds according to the invention are blockers of the voltage  
dependent sodium channels and/or calcium channels. These compounds  
therefore displace 3H-batrachotoxin (BTX) with a high affinity from the  
10 binding site on the sodium channel, with  $IC_{50}$  in the low  $\mu M$  or sub  $\mu M$  range.  
Similarly the compounds displace 3H-nitrendipine from the binding site in the  
calcium channel, with  $IC_{50}$  in the low  $\mu M$  or most usually in the sub  $\mu M$  range  
as well as inhibiting calcium influx induced through calcium channels via  
cellular depolarisation.

15 Such substances exhibit "use-dependency" when the sodium channels  
are blocked i.e. maximum blockage of the sodium channels is only achieved  
after repeated stimulation of the sodium channel. Consequently, the  
substances preferably bind to sodium channels which are multiply activated.  
As a result the substances are capable of activity preferentially in those  
20 regions of the body which are pathologically over-stimulated, as illustrated by  
patch-clamp experiments (W.A. Catterall, Trends Pharmacol. Sci., 8, 57-65;  
1987) which show that the compounds according to the invention block the  
electrically stimulated sodium channel in a "use-dependent" manner.

As a consequence of these mechanisms the compounds of the invention  
25 are active *in vivo* when orally administered in the range of 0.1 to 100 mg/kg in  
a wide range of animal models and in particular in the MES test of  
electrically-induced convulsions, in the formalin model of persistent pain and  
in the carragenan model of inflammation.

In view of the above described mechanisms of action, the compounds of the present invention are useful in the treatment or prevention of neuropathic pain. Neuropathic pain syndromes include, and are not limited to: diabetic neuropathy; sciatica; non-specific lower back pain; multiple sclerosis pain; 5 fibromyalgia; HIV-related neuropathy; neuralgia, such as post-herpetic neuralgia and trigeminal neuralgia; and pain resulting from physical trauma, amputation, cancer, toxins or chronic inflammatory conditions.

Compounds of the invention are also useful for the treatment of chronic pain. Chronic pain includes, and is not limited to, chronic pain caused by 10 inflammation or an inflammatory-related condition, osteoarthritis, rheumatoid arthritis or as sequela to disease, acute injury or trauma and includes upper back pain or lower back pain (resulting from systematic, regional or primary spine disease (such as radiculopathy), bone pain (due to osteoarthritis, osteoporosis, bone metastasis or unknown reasons), pelvic pain, 15 spinal cord injury-associated pain, cardiac chest pain, non-cardiac chest pain, central post-stroke pain, myofascial pain, cancer pain, AIDS pain, sickle cell pain, geriatric pain or pain caused by headache, temporomandibular joint syndrome, gout, fibrosis or thoracic outlet syndromes.

Compounds of the invention are also useful in the treatment of acute 20 pain (caused by acute injury, illness, sports-medicine injuries, carpal tunnel syndrome, burns, musculoskeletal sprains and strains, musculotendinous strain, cervicobrachial pain syndromes, dyspepsia, gastric ulcer, duodenal ulcer, dysmenorrhea, endometriosis or surgery (such as open heart or bypass surgery), post operative pain, kidney stone pain, gallbladder pain, gallstone 25 pain, obstetric pain or dental pain.

Compounds of the invention are also useful in the treatment of migraine, such as tension type headache, transformed migraine or evolutive headache, cluster headache, as well as secondary headache disorders, such as

the ones derived from infections, metabolic disorders or other systemic illnesses and other acute headaches, paroxysmal hemicrania and the like, resulting from a worsening of the above mentioned primary and secondary headaches.

5       Compounds of the invention are also useful for the treatment of neurological conditions and cognitive disorders. Neurological conditions include, and are not limited to, conditions such as epilepsy (including simple partial seizures, complex partial seizures, secondary generalised seizures, further including absence seizures, myoclonic seizures, clonic seizures, tonic  
10   seizures, tonic clonic seizures and atonic seizures), degenerative dementia (including senile dementia, Alzheimer's disease, Pick's disease, Parkinson's disease and vascular dementia (including multi-infarct dementia, stroke and cerebral ischemia), as well as dementia associated with intracranial space occupying lesions, trauma, infections and related conditions (including HIV  
15   infection), metabolism, toxins, anoxia and vitamin deficiency; and mild cognitive impairment associated with aging, particularly age associated memory impairment, movement disorders (postencephalitic parkinsonism, progressive supranuclear palsy, corticobasal degeneration), narcolepsy, deficit and hyperactivity disorders (ADHD), amyotrophic lateral sclerosis, Down's  
20   syndrome.

      Compounds of the invention are also useful for the treatment of psychiatric disorders. Psychiatric disorders include, and are not limited to, manic depression also known as bipolar disorder (such as bipolar disorder type I, bipolar disorder type II), cyclothymic disorder, rapid cycling, ultradian  
25   cycling, bipolar depression, acute mania, mania, mixed mania, hypomania or unipolar depression, schizophrenia, schizophreniform disorders, schizoaffective disorders, delusional disorders, brief psychotic disorders, shared psychotic disorders, psychotic disorder due to a general medical

condition, substance-induced psychotic disorders or a psychotic disorder not otherwise specified, anxiety disorders and moreover in smoke and drug addiction.

Compounds of the invention are also useful in the treatment of  
5 peripheral diseases such as tinnitus, muscle spasm, muscular sclerosis, and  
—other disorders, including, and not limited to cardiovascular diseases (such as  
cardiac arrhythmia, cardiac infarction or angina pectoris, hypertension,  
hypoxia, cardiac ischemia) endocrine disorders (such as acromegaly or  
diabetes insipidus), diseases in which the pathophysiology of the disorder  
10 involves excessive or hypersecretory or otherwise inappropriate cellular  
secretion of an endogeneous substance (such as catecholamine, a hormone or a  
growth factor).

Compounds of the invention are also useful in the treatment of liver  
disease, such as inflammatory liver disease, for example chronic viral hepatitis  
15 B, chronic viral hepatitis C, alcoholic liver injury, primary biliary cirrhosis,  
autoimmune hepatitis, non-alcoholic steatohepatitis and liver transplant  
rejection.

Compounds of the invention inhibit inflammatory processes affecting  
all body systems. Therefore are useful in the treatment of inflammatory  
20 processes of the muscular-skeletal system of which the following is a list of  
examples but it is not comprehensive of all target disorders: arthritic  
conditions such as alkylosing spondylitis, cervical arthritis, fibromyalgia, gut,  
juvenile rheumatoid arthritis, lumbosacral arthritis, osteoarthritis,  
osteoporosis, psoriatic arthritis, rheumatic disease; disorders affecting skin  
25 and related tissues: eczema, psoriasis, dermatitis and inflammatory conditions  
such as sunburn; disorders of the respiratory system: asthma, allergic rhinitis  
and respiratory distress syndrome, lung disorders in which inflammation is  
involved such as asthma and bronchitis; chronic obstructive pulmonary



disease; disorders of the immune and endocrinological systems: periarteritis nodosa, thyroiditis, aplastic anaemia, sclerodoma, myasthenia gravis, multiple sclerosis, sarcoidosis, nephritic syndrome, Bechet's syndrome, polymyositis, gingivitis.

5           Compounds of the invention are also useful in the treatment of gastrointestinal (GI) tract disorders such as inflammatory bowel disorders including but not limited to ulcerative colitis, Crohn's disease, ileitis, proctitis, celiac disease, enteropathies, microscopic or collagenous colitis, eosinophilic gastroenteritis, or pouchitis resulting after proctocolectomy and  
10 post ileonatal anastomosis, and irritable bowel syndrome including any disorders associated with abdominal pain and/or abdominal discomfort such as pylorospasm, nervous indigestion, spastic colon, spastic colitis, spastic bowel, intestinal neurosis, functional colitis, mucous colitis, laxative colitis and functional dyspepsia; but also for treatment of atrophic gastritis, gastritis  
15 varialoforme, ulcerative colitis, peptic ulceration, pyresis, and other damage to the GI tract, for example, by *Helicobacter pylori*, gastroesophageal reflux disease, gastroparesis, such as diabetic gastroparesis; and other functional bowel disorders, such as non-ulcerative dyspepsia (NUD); emesis, diarrhea, and visceral inflammation.

20           Compounds of the invention are also useful in the treatment of disorders of the genito-urinary tract such as overactive bladder, prostatitis (chronic bacterial and chronic non-bacterial prostatitis), prostatic dysnia, interstitial cystitis, urinary incontinence and benign prostatic hyperplasia, annexities, pelvic inflammation, bartolinites and vaginitis.

25           Compounds of the invention are also useful in the treatment of ophthalmic diseases such as retinitis, retinopathies, uveitis and acute injury to the eye tissue, macular degeneration or glaucoma, conjunctivitis.

Compounds of the invention are also useful in the treatment of obesity.

Compounds of the invention are also useful for the treatment of all other conditions mediated by the inhibition of voltage gated sodium channels and/or voltage gated calcium channels.

It will be appreciated that the compounds of the invention may advantageously be used in conjunction with one or more other therapeutic agents. Examples of suitable agents for adjunctive therapy include a 5HT<sub>1B/1D</sub> agonist, such as a triptan (e.g. sumatriptan or naratriptan); an adenosine A<sub>1</sub> agonist; an EP ligand; an NMDA modulator, such as a glycine antagonist; a substance P antagonist (e.g. an NK1 antagonist); a cannabinoid; acetaminophen or phenacetin; a 5-lipoxygenase inhibitor; a leukotriene receptor antagonist; a DMARD (e.g. methotrexate); gabapentin and related compounds; a tricyclic antidepressant (e.g. amitriptyline); a neurone stabilising antiepileptic drug; a monoaminergic uptake inhibitor (e.g. venlafaxine); a matrix metalloproteinase inhibitor; a nitric oxide synthase (NOS) inhibitor, such as an iNOS or an nNOS inhibitor; an inhibitor of the release, or action, of tumor necrosis factor alpha; an antibody therapy, such as monoclonal antibody therapy; an antiviral agent, such as a nucleoside inhibitor (e.g. (lamivudine) or an immune system modulator (e.g. interferon); an analgesic, such as a cyclooxygenase-2 inhibitor; a local anaesthetic; a stimulant, including caffeine; an H<sub>2</sub>-antagonist (e.g. ranitidine); a proton pump inhibitor (e.g. omeprazole); an antacid (e.g. aluminium or magnesium hydroxide); an antifatulent (e.g. simethicone); a decongestant (e.g. phenylephrine, phenylpropanolamine, pseudoephedrine, oxymetazoline, epinephrine, naphazoline, xylometazoline, propylhexedrine, or levodesoxyephedrine, naphazoline, xylometazoline, propylhexedrine, or levodesoxyephedrine); antitussive (e.g. codeine, hydrocodone, carmiphen, carbetapentane, or dexamethorphan); a diuretic; or a sedating or non-sedating antihistamine. It is to be understood that the present invention covers

the use of a compound of formula (I) or a pharmaceutically acceptable salt thereof in combination with one or more therapeutic agents.

The compounds of the present invention are useful in human and veterinary medicine. It is to be understood that reference to treatment includes  
5 both treatments of established symptoms and prophylactic treatment, unless explicitly stated otherwise.

The cyclopentyl derivatives of general formula I as above defined can be administered as the "active ingredient" of a pharmaceutically acceptable composition which can be prepared by conventional procedures, for instance  
10 by mixing the active ingredient with pharmaceutically acceptable, therapeutically inert organic and/or inorganic carrier materials.

The composition comprising the above defined cyclopentyl derivatives can be administered in a variety forms, e.g. orally, in the form of tablets, troches, capsules, sugar or film coated tablets, liquid solutions, emulsions or  
15 suspensions; rectally, in the form of suppositories; parenterally, e.g. by intramuscular or intravenous injection or infusion; and transdermally.

Suitable pharmaceutically acceptable, therapeutically inert organic and/or inorganic carrier materials useful in the preparation of such composition include, for example, water, gelatin, gum arabic, lactose, starch,  
20 cellulose, magnesium stearate, talc, vegetable oils, polyalkyleneglycols and the like. The composition comprising the cyclopentyl derivatives of formula I as above defined can be sterilized and may contain further well known components, such as, for example, preservatives, stabilizers, wetting or emulsifying agents, e.g. paraffin oil, mannide monooleate, salts to adjust  
25 osmotic pressure, buffers and the like.

For example, the solid oral forms may contain, together with the active ingredient, diluents, e.g. lactose, dextrose, saccharose, cellulose, corn starch or potato starch; lubricants, e.g. silica, talc, stearic acid, magnesium or

calcium stearate, and/or polyethylene glycols; binding agents, e.g. starches, arabic gums, gelatin, methylcellulose, carboxymethylcellulose or polyvinyl pyrrolidone; disgregating agents, e.g. a starch, alginic acid, alginates or sodium starch glycolate; effervescing mixtures; dyestuffs; sweeteners; wetting agents such as lecithin, polysorbates, laurylsulphates; and, in general, non-toxic and pharmacologically inactive substances used in pharmaceutical formulations. Said pharmaceutical preparations may be manufactured in known manner, for example, by means of mixing, granulating, tableting, sugar-coating, or film-coating processes.

- 10 The oral formulations comprise sustained release formulations that can be prepared in conventional manner, for instance by applying an enteric coating to tablets and granules.

The liquid dispersion for oral administration may be e.g. syrups, emulsions and suspensions.

- 15 The syrups may contain as carrier, for example, saccharose or saccharose with glycerine and/or mannitol and/or sorbitol.

- Suspensions and emulsions may contain as a carrier, for example, a natural gum, agar, sodium alginate, pectin, methylcellulose, carboxymethylcellulose, or polyvinyl alcohol. The suspensions or solutions for intramuscular injections may contain, together with the active compound, a pharmaceutically acceptable carrier, e.g. sterile water, olive oil, ethyl oleate, glycols, e.g. propylene glycol, and, if desired, a suitable amount of lidocaine hydrochloride. The solutions for intravenous injections or infusion may contain as carrier, for example, sterile water or preferably they may be in the form of sterile, aqueous, isotonic saline solutions.
- 20  
25

The suppositories may contain, together with the active ingredient, a pharmaceutically acceptable carrier, e.g. cocoa butter, polyethylene glycol, a polyoxyethylene sorbitan fatty acid ester surfactants or lecithin.

Suitable treatment is given 1, 2 or 3 times daily, depending upon clearance rate. Accordingly, the desired dose may be presented in a single dose or as divided doses administered at appropriate intervals, for example two to four or more sub-doses per day.

5        The pharmaceutical compositions comprising the cyclopentyl derivatives of formula I as above defined will contain, per dosage unit, e.g., capsule, tablet, powder injection, teaspoonful, suppository and the like from about 0.1 to about 500 mg of the active ingredient most preferably from 1 to 10 mg.

10        Optimal therapeutically effective doses to be administered may be readily determined by those skilled in the art and will vary, basically, with the strength of the preparation, with the mode of administration and with the advancement of the condition or disorder treated. In addition, factors associated with the particular subject being treated, including subject age, weight, diet and time of administration, will result in the need to adjust the  
15        dose to an appropriate therapeutically effective level.

The following Examples further illustrate the invention.

Example 1

20        *cis*-2-[3-(2-Fluoro-benzyloxy)-benzylamino]-cyclopentanecarboxylic acid amide

A 2M solution of 2-amino-cyclopentanecarboxylic acid amide (0.75 g, 6.5 mmol) in dry THF was added to a 1M solution in dry THF of 3-(2-fluoro-benzyloxy)-benzaldehyde (1.64 g, 7.15 mmol), prepared as described in Example 3. To this mixture, a 2M solution of Ti(O-*i*Pr)<sub>4</sub> (2.77 g, 9.75 mmol)  
25        in dry THF was added dropwise and the reaction mixture was stirred 12 hours at room temperature under nitrogen.

A 0.75M solution of sodium borohydride (0.69 g, 18.2 mmol) in absolute ethanol was added and the resulting mixture was heated at 70°C for 6

19

hours. After cooling, 8 ml of water was added to quench the reaction and the resulting white precipitate was removed by filtration. The crude compound was purified using SCX cartridge (Strong Cation eXchange resin). The pure product was recovered by eluting with 3% ammonia solution in methanol. The title compound was obtained (2.08 g) after evaporating the solvent under vacuum with a final yield of 94%.

MS (ESI Pos Spray 3.5 kV; Skimmer 20 V; Probe 250°C): 343 [MH<sup>+</sup>]

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) δ: 7.55 (m, 1H), 7.45 (m, 2H), 7.25 (m, 3H), 7.0 (s, 1H), 6.88 (m, 2H), 6.78 (s, 1H), 5.1 (s, 2H), 3.7 (dd, 2H), 3.10 (m, 1H), 2.65 (m, 1H), 1.90-1.4 (m, 6H).

#### Example 2

*cis*-2-[4-(2-Fluoro-benzyloxy)-3,5-dimethyl-benzylamino]-cyclopentanecarboxylic acid amide

A 2M solution of 2-amino-cyclopentanecarboxylic acid amide (0.75 g, 6.5 mmol) in dry THF was added to a 1M solution in dry THF of 4-(2-fluoro-benzyloxy)-3,5 dimethyl-benzaldehyde (1.84 g, 7.15 mmol), prepared as described in Example 4. To this mixture, a 2M solution of Ti(O-*i*Pr)<sub>4</sub> (2.77 g, 9.75 mmol) in dry THF was added dropwise and the reaction mixture was stirred 12 hours at room temperature under nitrogen.

A 0.75M solution of sodium borohydride (0.69 g, 18.2 mmol) in absolute ethanol was added and the resulting mixture was heated at 70°C for 6 hours. After cooling, 8 ml of water was added and the resulting white precipitate was removed by filtration. The crude compound was purified using SCX cartridge (Strong Cation eXchange resin). The pure product was recovered by eluting with 3% ammonia solution in methanol. The title compound was obtained (2.14 g) after evaporating the solvent under vacuum with a yield of 89%.

MS (ESI Pos Spray 3.5 kV; Skimmer 20 V; Probe 250°C): 371 [MH<sup>+</sup>]

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) δ: 7.60 (m, 1H), 7.48 (m, 2H), 7.28 (m, 2H), 6.95 (s, 2H), 6.78 (s, 1H), 4.80 (s, 2H), 3.6 (dd, 2H), 3.15 (m, 1H), 2.68 (m, 1H), 2.2 (s, 6H), 1.85-1.51 (m, 6H).

### Example 3

#### 5      **3-(2-Fluoro-benzyloxy)-benzaldehyde**

0.5M solution of 1-bromomethyl-2-fluoro-benzene (1.50 g, 8.0 mmol) in DMF was added dropwise to a suspension of 3-hydroxy-benzaldehyde (0.89 g, 7.3 mmol), K<sub>2</sub>CO<sub>3</sub> (1.51 g, 11 mmol) and KI (0.12 g, 0.73 mmol) in 100 ml DMF. The reaction mixture was stirred at 90°C overnight. After cooling to  
10 room temperature, the solid residue was filtered off and the solvent was evaporated under vacuum. The residue was dissolved in ethyl acetate, the organic layer washed twice with 1M NaOH, dried over Na<sub>2</sub>SO<sub>4</sub> and evaporated to dryness. The residue was purified on silica gel, obtaining 167 mg of the title compound (quantitative yield).

#### 15      Example 4

#### 4-(2-Fluoro-benzyloxy)-3,5-dimethyl-benzaldehyde

0.5M Solution of 1-bromomethyl-2-fluoro-benzene (1.50 g, 8.0 mmol) in DMF was added dropwise to a suspension containing 1.09 g of 4-hydroxy-3,5-dimethyl-benzaldehyde (7.3 mmol), 1.51 g of K<sub>2</sub>CO<sub>3</sub> (11 mmol) and 120  
20 mg of KI (0.73 mmol) in 100 ml DMF. The reaction followed the same procedure described in Example 3. The residue was purified on silica gel, obtaining a quantitative recovery of the title compound. (1.88 g)

### Example 5

#### *In vitro* binding of <sup>3</sup>H-batrachotoxin in rat brain membranes

25      Membrane preparations (P2 fraction) Male Wistar rats (Harlan, Italy – 175-200 g) were sacrificed under light anaesthesia and brains were rapidly removed and cortex was dissected out, homogenized in 10 vol. of ice-cold 0.25 M sucrose buffer (50 mM Tris-HCl, pH 7.4). The crude homogenate was

centrifuged at 3250 rpm for 10 min and the supernatant recovered. The pellet was homogenized and centrifuged again and the two supernatants were pooled and centrifuged at 14750 rpm for 10 min, +4°C. The resulting pellet was stored at -20°C until use.

5        Binding assay. The pellet was resuspended in 50 mM Hepes buffer, pH 7.4 containing 0.8 mM MgSO<sub>4</sub>, 5.4 mM KCl, 5.5 mM glucose and 130 mM choline using Polytron PT10. The binding assay was carried out in 0.25 ml final volume containing 50 µl of membrane preparation (ca 200 µg of protein), 50 µl of <sup>3</sup>H-batrachotoxin ligand (10 nM), 50 µl of TTX (1 µM), 50 µl of  
10    scorpion toxin (37.5 µg/ml) and 50 µl of test compound or buffer or 300 µM of veratridine to determine non specific binding. The binding assay was performed at 37°C for 30 min and stopped by rapid filtration under vacuum through Whatman GF/B glass fiber filters. Filters (pre-soaked with polyethylenimine 0.1%) were washed with 3x5 ml of ice-cold buffer and  
15    placed in picovials containing scintillation cocktail (Filter Count, Packard). Radioactivity bound was measured by liquid scintillation spectrometry at 45% efficiency.

Data analysis. The IC<sub>50</sub> was calculated from displacement curves by computer program LIGAND (McPherson, J. Pharmacol. Methods, 14, 213.  
20    1985). The displacement curves were obtained using at least 9 concentrations, each in duplicate, covering a 100000 fold range.

#### Example 6

##### In vitro binding of <sup>3</sup>H-nitrendipine in rat brain membranes

Membrane preparations Male Wistar rats (Harlan, Italy – 175-200 g) were  
25    sacrificed under light anaesthesia and brains were rapidly removed and cortex was dissected out, homogenized in 10 vol. of ice-cold 50 mM Tris-HCl, pH 7.7 using Polytron PT10. The crude homogenate was centrifuged at 50000xg for 10 min. The pellet was homogenized and centrifuged twice in fresh buffer at



50000xg for 10 min, +4°C. The resulting pellet was stored at -20°C until use.

Binding assay. The pellet was resuspended in 50 mM Tris·HCl, pH 7.7 using Polytron PT10. The binding assay was carried out in 1 ml final volume containing 900 µl of membrane preparation (ca 700 µg of protein), 50 µl of <sup>3</sup>H-nitrendipine (0.15 nM), and 50 µl of test compound or buffer or 1 µM of nifedipine to determine non specific binding. The binding assay was performed at 25°C for 45 min and stopped by rapid filtration under vacuum through Whatman GF/B glass fiber filters. Filters were washed with 3x5 ml of ice-cold buffer and placed in picovials containing scintillation cocktail (Filter Count, Packard). Radioactivity bound was measured by liquid scintillation spectrometry at 45% efficiency.

Data analysis. The IC<sub>50</sub> was calculated from displacement curves by computer program LIGAND (McPherson, J. Pharmacol. Methods, 14, 213, 1985). The displacement curves were obtained using at least 9 concentrations, each in duplicate, covering a 100000 fold range.

#### Example 7

##### **Calcium influx assay**

IMR32 human neuroblastoma cells constitutively possess both L and N type channels. Under differentiating conditions, IMR32 preferentially express on the membrane surface N- type calcium channels. The remaining L-type calcium channels were blocked using the selective L type blocker, nifedipine. In these experimental conditions, only N type channels can be detected.

IMR32 cells were differentiated using 1mM dibutyryl-cAMP and 2.5 µM bromodeoxyuridine for 8 days (4 times) in 225 cm<sup>2</sup> flask, then detached, seeded at 200,000 cells/well on 96 polyllysine-coated plates and further incubated for 18-24 h in the presence of differentiating buffer before use.

The Ca<sup>2+</sup> Kit Assay (Molecular Devices), based on a fluorescent calcium indicator 485-535 nm wavelength, was used.

23

Differentiated cells were incubated with dye loading for 30 min at 37°C then, nifedipine alone (1  $\mu$ M) or in the presence of  $\omega$ -conotoxin or test compounds were added for further 15 min.

The fluorescence (485-535nm) was measured before and after (30-40 sec) the automated injection of 100 mM KCl depolarizing solution using a Victor plate reader (Perkin Elmer).

#### Example 8

##### **Maximal electroshock test in rats and mice**

Wistar rats received an electroshock (160 mA for 0.2 s with a pulse train of 60 Hz having a pulse duration of 0.4 ms; ECT unit model 7801, Ugo Basile, Comerio, Italy) through intra-aural clip electrodes sufficient to produce a hindlimb tonic extensor response in at least 97% of control animals.

Mice received a 28 mA shock of 0.7 s with a pulse train of 80 Hz having a pulse duration of 0.4 ms. Several doses of the test compound and standard AEDs were administered to groups of 10 to 20 mice or rats per dose in a volume of 5 ml/kg 60 min p.o. or 30 min i.p. before induction of MES to calculate ED<sub>50</sub> values. The complete suppression of the hindlimb tonic extensor component of seizures was taken as evidence of anticonvulsant activity.

#### Example 9

##### **Mice Formalin Test**

According to a modified protocol from Rosland et al., (1990) mice were injected subcutaneously (s.c.) with 20  $\mu$ l of 2.7% solution of formalin into the plantar surface of left hindpaw and placed immediately into clear PVC observation chambers (23 x 12 x 13 cm). Pain behaviour was quantified by counting the cumulative licking time (s) of the injected paw. Measurements were taken during the early phase (0-5 min) and late phase (30-40 min) after formalin injection (Tjolsen et al. 1992).

The test compound was administered p.o. 15 min before formalin

injection in a volume of 10 ml/kg body weight to groups of 10 mice per dose.  
Control group was treated with vehicle.

Example 10

**Carragenan model of inflammation**

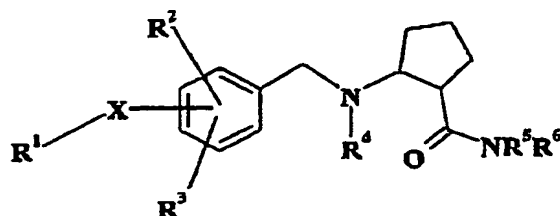
5 Male Wistar rats of 175-200 grams were used.

The left hind paw was injected with 100 µl of carrageenan (2% w/v in saline). Compounds of the invention (30 mg/kg), indomethacin (5 mg/kg) or control vehicle (such as distilled water) were orally administered 1 h before carrageenan injection. The paw volume was measured with a plethysmometer  
10 (Ugo Basile) immediately before (basal) and 1, 2, 3, 4 and 5 h after the carrageenan injection.

25

**CLAIMS**

1. A compound of formula I



I

wherein

X is methylene, oxygen, sulphur or a NR<sup>7</sup> group;

R<sup>1</sup> is a straight or branched C<sub>1</sub>-C<sub>8</sub> alkyl or C<sub>3</sub>-C<sub>8</sub> alkenylene or C<sub>3</sub>-C<sub>8</sub> alkynylene chain, optionally substituted with CF<sub>3</sub>, phenyl, phenoxy or naphthyl, the aromatic rings optionally substituted by one or more C<sub>1</sub>-C<sub>4</sub> alkyl, halogens, trifluoromethyl, hydroxy or C<sub>1</sub>-C<sub>4</sub> alkoxy groups;

R<sup>2</sup>, R<sup>3</sup> are independently hydrogen, a C<sub>1</sub>-C<sub>3</sub> alkyl chain, halogen, trifluoromethyl, hydroxy or C<sub>1</sub>-C<sub>4</sub> alkoxy groups;

R<sup>4</sup>, R<sup>5</sup>, R<sup>6</sup>, R<sup>7</sup> are independently hydrogen or C<sub>1</sub>-C<sub>6</sub> alkyl; and the pharmaceutically acceptable salts thereof.

2. Compounds of formula (I) according to claim 1, wherein X is oxygen, methylene, NH or NCH<sub>3</sub>, R<sup>1</sup> is C<sub>1</sub>-C<sub>8</sub> alkyl chain, optionally substituted with CF<sub>3</sub>, phenyl or phenoxy group, where the aromatic ring in R<sup>1</sup> is optionally substituted by one or two halogen or methoxy or trifluoromethyl groups, R<sup>2</sup> and R<sup>3</sup> are hydrogen, methyl, methoxy, fluorine, chlorine or bromine, R<sup>4</sup>, R<sup>5</sup> and R<sup>6</sup> are hydrogen or methyl.

3. A compound selected from the group consisting of:

- 2-(2-benzyloxy-benzylamino)-cyclopentane carboxylic acid amide;  
2-(3-benzyloxy-benzylamino)-cyclopentane carboxylic acid amide;  
2-(4-benzyloxy-benzylamino)-cyclopentane carboxylic acid amide;  
2-[2-(2-Fluoro-benzyloxy)-benzylamino]-cyclopentane carboxylic acid  
5 amide;  
2-[3-(2-Fluoro-benzyloxy)-benzylamino]-cyclopentane carboxylic acid  
amide;  
*cis*-2-[3-(2-Fluoro-benzyloxy)-benzylamino]-cyclopentane carboxylic  
acid amide;  
10 2-[4-(2-Fluoro-benzyloxy)-benzylamino]-cyclopentane carboxylic acid  
amide;  
2-[4-(2-Fluoro-benzylthio)-benzylamino]-cyclopentane carboxylic acid  
amide;  
2-[4-(2-Fluoro-benzylamino)-benzylamino]-cyclopentane carboxylic  
15 acid amide;  
2-[2-(2-Fluoro-benzyloxy)-3-fluoro-benzylamino]-cyclopentane  
carboxylic acid amide;  
2-[4-(2-Fluoro-benzyloxy)-3-fluoro-benzylamino]-cyclopentane  
carboxylic acid amide;  
20 2-[2-(2-Fluoro-benzyloxy)-3-chloro-benzylamino]-cyclopentane  
carboxylic acid amide;  
(2-[4-(2-Fluoro-benzyloxy)-3-chloro-benzylamino]-cyclopentane  
carboxylic acid amide;  
(2-[4-(2-Fluoro-benzyloxy)-3-bromo-benzylamino]-cyclopentane  
25 carboxylic acid amide;  
(2-[4-(2-Fluoro-benzyloxy)-2-methoxy-benzylamino]-cyclopentane  
carboxylic acid amide;  
(2-[4-(2-Fluoro-benzyloxy)-3-methoxy-benzylamino]-cyclopentane

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carboxylic acid amide;

2-[4-(2-Fluoro-benzyloxy)-3,5-dimethyl-benzylamino]-cyclopentane

carboxylic acid amide;

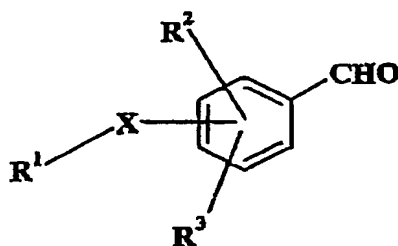
*cis*-2-[4-(2-Fluoro-benzyloxy)-3,5-dimethyl-benzylamino]-cyclopentane

5 carboxylic acid amide;

and all the stereoisomers and/or pharmaceutically acceptable salts thereof.

4. A process for the preparation of a compound of formula I, as defined in claim 1, or a pharmaceutically acceptable salt thereof, the process comprising:

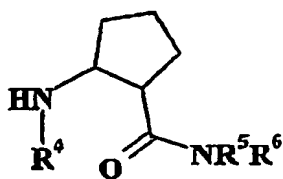
a) reaction of a compound of formula II



II

wherein  $R^1$ ,  $R^2$ ,  $R^3$  and X are as defined above

with compounds of formula III, in the presence of a reducing agent

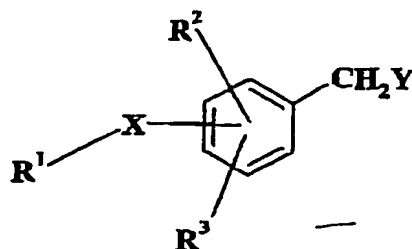


III

wherein  $R^4$ ,  $R^5$  and  $R^6$  are as defined previously thus obtaining a compound of formula I; or

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b) reaction of compounds of formula IV

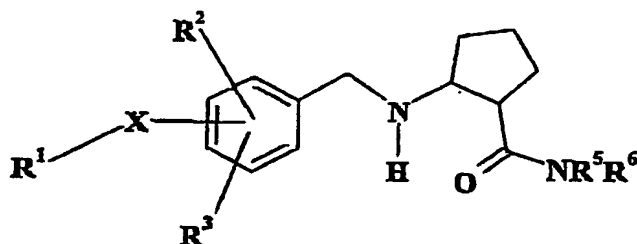


IV

5 wherein  $X$ ,  $R^1$ ,  $R^2$  and  $R^3$  are as defined above and  $Y$  is a halogen atom or a O-EWG group, where the EWG means an electron withdrawing group, like e.g. mesyl, tosyl or trifluoroacetyl groups, able to transform the oxygen

10 with compounds of formula III thus obtaining a compound of formula I; or

c) reacting of a compound of formula Ia



Ia

15 wherein  $R^1$ ,  $R^2$ ,  $R^3$ ,  $R^5$ ,  $R^6$  and  $X$  are as defined above, with compounds of formula V or VI



20 wherein  $Y$  and  $R^4$  are as defined above; and  $R^8$  is hydrogen or  $C_1-C_5$  alkyl, thus obtaining a compound of the invention in which  $R^4$  is  $C_1-C_6$  alkyl; and, if

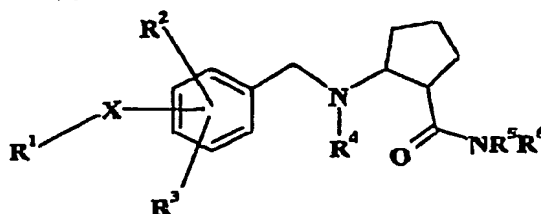
desired, converting a compound of the invention into another compound of the invention and/or, if desired, converting a compound of the invention into a pharmaceutically acceptable salt and/or, if desired, converting a salt into a free compound and/or, if desired, separating a mixture of isomers of compounds of the invention into a single isomer.

5. A pharmaceutical composition containing a compound of formula I, as defined in claim 1, or a pharmaceutically acceptable salt thereof in admixture with a suitable carrier and/or diluent and optionally to other therapeutic agents.
- 10 6. The use of a compound of formula I, as defined in claim 1, or a pharmaceutically acceptable salt thereof, for the preparation of a medicament having sodium and/or calcium channel modulating activity for preventing, alleviating and curing neurological, psychiatric, cardiovascular, inflammatory, ophthalmic, urologic, metabolic and gastrointestinal diseases, where sodium
- 15 and/or calcium channels are involved in the pathological process.



**ABSTRACT****CYCLOPENTYL DERIVATIVES**

This invention is related to novel cyclopentyl derivatives of the  
 5 following general formula (I)

**I**

wherein

**X**

is methylene, oxygen, sulphur or a  $\text{NR}^7$  group;

10

**R<sup>1</sup>**

is a straight or branched  $\text{C}_1\text{-C}_8$  alkyl or  $\text{C}_3\text{-C}_8$  alkenylene or  $\text{C}_3\text{-C}_8$  alkynylene chain, optionally substituted with  $\text{CF}_3$ , phenyl, phenoxy or naphthyl, the aromatic rings optionally substituted by one or more  $\text{C}_1\text{-C}_4$  alkyl, halogens, trifluoromethyl, hydroxy or  $\text{C}_1\text{-C}_4$  alkoxy groups;

15

**R<sup>2</sup>, R<sup>3</sup>**

are independently hydrogen, a  $\text{C}_1\text{-C}_3$  alkyl chain, halogen, trifluoromethyl, hydroxy or  $\text{C}_1\text{-C}_4$  alkoxy groups;

**R<sup>4</sup>, R<sup>5</sup>, R<sup>6</sup>, R<sup>7</sup>**

are independently hydrogen or  $\text{C}_1\text{-C}_6$  alkyl;

20

and the pharmaceutically acceptable salts thereof that are active as sodium and/or calcium channel modulators and therefore useful in preventing, alleviating and curing a wide range of pathologies, including, but not limited to, neurological, psychiatric, cardiovascular, inflammatory, ophthalmic, urologic, metabolic and gastrointestinal diseases, where the above  
 25 mechanisms have been described as playing a pathological role.



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**Request for grant of a European Patent:**

**CYCLOPENTYL DERIVATIVES**

in the name of: **NEWRON PHARMACEUTICALS S.p.A.**

Our ref.: **SCB 1313 EUR/FM/cgr**

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